REMARKS

In the Office Action mailed November 12, 2002:

Claims 32, 33 and 35 were objected to as being dependent upon a rejected base claim, but were indicated to be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 4, 6 and 25 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 11-15, 26-28 and 31 were rejected under 35 U.S.C. 102(b) as being anticipated by Say et al.(U.S. Patent 6,134,461).

Claims 10, 18-24, 34, 36 and 37 were rejected under 35 U.S.C. 103(a) as being unpatentable over Say et al. in view of the Kim et al. article entitled: "Needle-Shaped Glucose Sensor with Multi-Cell Electrode Fabricated by Surface Micro Machining."

Claims 11 and 25 were rejected under 35 U.S.C. 103(a) as being unpatentable over Say et al.

Claims 16 and 17 were rejected under 35 U.S.C. 103(a) as being unpatentable over Say et al. in view of Meade et al. (U.S. Patent 5,770,369).

Claims 32, 33 and 35 have been rewritten as claims 48, 49 and 50, respectively.

New claims 51-55 have been added.

In response to the Examiner's comments in the first paragraph of the Office Action concerning incorrect identification of two patents in the IDS, applicants have reviewed the IDS and determined that "6,386,104-B1" should read 6,306,104-B1-- and "6,369,888-B1" should read --6,360,888-B1--. Further, applicants note that "6,152,899" should read --6,152,889--. A corrected IDS is submitted herewith along with a copy of each patent and publication. The Examiner is requested to consider the references and make them of record.

This is to confirm the election of the claims of Group I, claims 1-28 and 31-37 for prosecution in the above-identified application.

With respect to the election of species, applicant elects to prosecute Species I, drawn to Figure 1. The following claims read on Species I: 1-28, 31-37 and newly added claims 48-55.

With respect to the rejection of certain claims under 35 U.S.C. § 112, second paragraph, applicants make the following remarks. With respect to claim 4, paragraph 0096 of the application states that the convergence of the microprobe taper may be uniform as shown in Fig. 1A or non-uniform as shown in Fig. 2A. Even if the taper is non-uniform, it is apparent from Fig. 2A that the taper can be continuous. In the interest of expediting prosecution, applicants have amended claim 4 to delete the limitation that the taper is non-

uniform. Claim 6 has been amended to state that the minimum X dimension is 0.5 mm. This language is found at page 11, line 6 of the specification. Claim 25 has been made dependent on claim 12 to provide a proper antecedent the signal carrier.

In the last paragraph of claim 1, the article "a" has been inserted; and at several places in claim 12 articles have been inserted. It is respectfully submitted that these changes merely improve the readability of the claims and do not alter their scope.

The invention recited in claims 1-27, 31, 34, 36 and 37 relates to a microprobe having a body portion and a microprobe portion formed on a silicon substrate and a biosensor that is integrated into the silicon substrate.

This structure is not disclosed or suggested in Say et al., USP 6,134,461. Say et al. disclose a sensor that is formed on "a variety of non-conducting materials, including, for example, polymeric or plastic materials and ceramic materials." Col. 7, lines 52-54. The ceramic materials include aluminum oxide and silicon dioxide. Col. 8, lines 14-15. Nowhere do Say et al. disclose or suggest that the substrate should be silicon as claimed by applicants in all of claims 1-27, 31, 34, 36 and 37.

Applicants' invention is directed to an integrated biosensor microprobe that is small enough that it can be inserted into the skin with little or no pain. As noted at pages 1 and 2 of the specification, there is a major unmet need for one-step, painless testing of blood constituents to diagnose and control disease. Technology has brought about many changes in how assays are conducted, but the practice of phlebotomy, itself, has changed very little, and still consists of producing a drop of blood by a finger or arm stick using a metal lancet or drawing venous blood via hypodermic needle. A metal lancet is large and lancing is painful, particularly in the finger. The skin of infants and the elderly is fragile and is readily damaged by the lancet.

Diabetic home self-testing of blood glucose levels represents a major segment of the blood testing market. In 1993, the NIH Diabetes Control and Complications Trial showed that frequent testing (4-5 times daily) significantly reduced the serious complications of diabetes, but found that patient compliance was poor, in large part because of the pain involved. A number of approaches have been taken to solve this problem: including development of implantable continuous monitoring systems and introduction of meters designed to use blood from the arm. Continuous monitoring will permit excellent control of blood glucose levels. However, most currently available systems require medical assistance and insertion devices to implant and remove the sensor, with attendant cost and pain. Sensor performance and lifetime are still inadequate.

Sampling from alternate sites of the body such as the arm is somewhat less painful because of a lower density of nerve endings at these sites. However, because of differences

in skin microvasculature, the amount of blood produced is significantly smaller than from a fingerstick. More sensitive analytical techniques must be used. Many diabetics suffer from poor eyesight and calloused fingers as a result of their disease. With alternate site testing, the problem of getting the sample onto the test strip is actually intensified because of the difficulty in seeing the small volume and aligning the test strip with it. Automatic one-step meters have been introduced, but these have had difficulty with accurate collection and analysis of the small blood sample and still use a metal lancet, thus causing pain.

Applicant's initial research proposals met with skepticism. In 1998, a National Institutes of Health reviewer who is an expert in metal hypodermic needles commented that a silicon microprobe would require an unrealistically complex low-inertial injector to avoid fracture, which would occur with a displacement of a few microns. The reviewer stated that the proposed silicon device would be "two orders of magnitude" more costly "and in all respects inferior" to a plastic/steel microsampler.

More recently, however, others have come to recognize the advantages of a silicon microprobe.

Applicant's small silicon microprobe permits painless access to a blood sample. The blood component of interest can be measured in vivo or a small blood volume transported reliably to an ex vivo biosensor. Used with a small hand-held instrument, sampling and readout are automatic. Silicon microfabrication techniques highly developed for the semiconductor industry permit tight control of microprobe dimensions to maximize strength. The use of a single wafer lowers unit production costs to the point that the microprobe can be used as an inexpensive disposable for a single measurement or for short-term continuous measurement.

In the absence of any suggestion in Say et al. that the substrate be made of silicon or that the sensor be integrated into the substrate, it is respectfully submitted that claim 1 is patentable over Say et al. Clams 2-19, 21-27, 34 and 36 and 37 are believed patentable for the same reason claim 1 is patentable.

Several of the dependent claims have been rejected as obvious over Say et al. in view of Kim et al. Kim et al. disclose a complex structure having multiple layers of silicon, silicon dioxide and metal. Specifically, as shown in the cross-section of Fig. 1, the structure includes a first layer of silicon, a first layer of silicon dioxide 3 microns thick, a second layer of silicon 6.5 microns thick, a second layer of silicon dioxide 1 micron thick, a layer of metal and a plasma-enhanced oxide upper layer identified as PEOX that is 5 micron thick. The abstract states that the metal layer "was deposited to improve bending characteristics of the sensor" as a reinforcing layer. Further, because Kim et al. state that the second silicon layer is

deposited on the first silicon dioxide layer, this second silicon layer cannot be single-crystal silicon.

After fabrication, the sacrificial oxide layer is removed, liberating the sensor device from the base silicon layer. Whatever might be the merits of the Kim et al. structure, it is apparent that this structure is not just a silicon substrate and it is clearly not a single crystal silicon substrate. Thus, the substitution of the Kim et al. multi-layer substrate for the silicon dioxide substrate of Say et al. still does not suggest applicants' silicon substrate.

Furthermore, applicants submit that one skilled in the art would not be prompted to combine the Say et al. and Kim et al. references or to substitute the Kim et al. structure for the silicon dioxide substrate of Say et al. as the Examiner has done. Say et al. emphasizes at column 7, lines 52 and 53 that the substrate "may be formed using a variety of non-conducting materials"; and he proceeds to identify polymeric or plastic materials and ceramics as suitable. The silicon layer of the Kim et al. device, however, is a semi-conducting material and is not plastic or polymeric or ceramic. Therefore, the Kim et al structure would not appear to be suitable for use in place of the Say et al. substrate.

Dependent claims 16 and 17 were rejected as obvious over Say et al. in view of Meade et al. Meade et al., however, does not make up for the failure of Say et al. to disclose the use of a silicon substrate as claimed by applicants.

Claims 51-56 have been added. These claims are believed patentable for the same reason claim 1 is patentable and for the following additional reasons. Independent claim 51 is similar to claim 1 but specifies that the microprobe tapers in width from the body end to the penetration end. Such a structure has been found to have added strength over alternative structures such as those shown in Say et al. and in Kim et al. where the probe has parallel sides over most of its extension. Accordingly, claim 51 and dependent claims 52-54 are believed patentable over these references. For the same reasons, dependent claims 2-5 are also believed patentable.

Claim 55 is similar to claim 51 and is believed patentable for the same reason. Claims 55 and 56 also recite that the silicon substrate is single crystal silicon. Since neither Say et al. nor Kim et al. discloses or suggests a microprobe formed in single crystal silicon, claims 55 and 56 are believed patentable over these references.

In view of the foregoing, applicants believe that all of the claims are now in condition for allowance and respectfully requests the Examiner to pass the subject application to issue. If for any reason the Examiner believes any of the claims are not in condition for allowance, he is encouraged to phone the undersigned at (650) 849-7777 so that any remaining issues may be resolved.

Aside for the fees for Petition to Extend Time and for the additional claims, no additional fee is believed due for filing this response. However, if a fee is due, please charge such fee to Pennie & Edmonds LLP's Deposit Account No. 16-1150.

Respectfully submitted,

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